

## Generation and Treatment of a Mouse Eye Model for Familial Dysautonomia

### Award Information

#### Agency:

Department of Health and Human Services

#### Amount:

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SBIR

#### Contract:

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#### Agency Tracking Number:

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### Small Business Information

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#### Hubzone Owned:

N

#### Woman Owned:

N

#### Socially and Economically Disadvantaged:

N

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### Research Institution

N/A

### Abstract

DESCRIPTION provided by applicant Familial Dysautonomia FD is a rare disease caused by an

intronic mutation in the inhibitor of kappa B kinase complex associated protein gene Ikbkap The mutation leads to nervous system specific exon skipping resulting in low levels of functional IKAP protein Patients with FD suffer from degeneration of the sensory and autonomic nervous system resulting in multiple neuropathies A devastating quality of life issue is the development of progressive blindness in adults due to optic nerve atrophy most likely due to the gradual loss of retinal ganglion cells RGCs Our goal for this Phase I proposal is to generate a mouse eye model of FD and obtain in vivo proof of concept of an innovative gene therapy to effectively treat retinal dysfunction The homozygous knockout of Ikbkap in mice is embryonic lethal thus conditional knockouts have been generated to study late embryonic and adult phenotypic effects on development To date none of the conditional knockouts have exhibited an eye phenotype most likely due to the use of promoters that do not target Cre recombinase to RGCs The following Aims are designed to generate a mouse eye model of FD as well as for assessing gene therapy approaches for safety and treatment to prevent optic nerve atrophy Aim Generate a mouse FD model of retinal optic nerve atrophy To generate a mouse model of retinal dysfunction we will use two approaches A Cross a Floxed Ikbkap mouse with a mouse that expresses Cre from the Math RGC precursor specific promoter and B Specifically express Cre in RGCs by targeted intravitreal injection of a Cre expressing adeno associated virus Aim Rescue of the retinal nerve atrophy in the mouse FD eye model Once the model from Aim is established the mice will be treated by subretinal or intravitreal injection with an Ikbkap expressing lentiviral construct that has been shown to rescue apoptosis of day E cultured mouse Ikbkap dorsal root ganglion neurons These studies will form the basis for our Phase II application to obtain preclinical data for filing an FDA IND for preventing blindness in patients with FD PUBLIC HEALTH RELEVANCE Patients with familial dysautonomia FD a severe neurodegenerative disease suffer from progressive blindness FD is caused by a mutation in the Ikbkap gene which leads to a loss of IKAP protein in neurons We have developed a gene therapy approach that restores IKAP and rescues cultured neurons The goal of this proposal is to develop a mouse eye model of FD and use gene therapy to rescue retinal dysfunction This proof of concept will allow progress towards clinical trials to alleviate a major quality of life condition suffered by patients with FD

\* information listed above is at the time of submission.